Effect of Age on Clinical Outcomes in Phase 1 Trial Participants

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Background: Most persons with cancer living in the United States are older than 65 years of age; however, in general, elderly persons are under-represented in clinical trials and outcomes data are lacking.

Methods: Outcomes data were analyzed of elderly participants (≥ 65 years of age) enrolled in phase 1 clinical trials and the results compared with those of younger patients. All consecutive, single-center, phase 1 oncology trials initiated and completed at the H. Lee Moffitt Cancer Center & Research Institute between 1997 and 2007 were included. Patient data (including survival, response, and toxicity rates) were extracted from a cancer registry database and electronic medical records at Moffitt Cancer Center.

Results: After excluding multi-institution trials, we analyzed 39 trials for a total of 1,162 enrolled study participants, 32.7% of whom were elderly. Among patients who underwent transplantation, median survival rates were worse in those who were elderly compared with those who were younger (44.9 vs 32.9 months; P = .0037). However, in the no-transplantation setting, participants who were elderly had a median survival rate of 10.9 months (95% confidence interval [CI]: 8.9–13.1) compared with 8.8 months (95% CI: 7.9–10.3) in those who were younger (P = .15). Both groups had similar overall response rates (15.2% vs 13.1%) and similar treatment-related mortality rates (1% vs 0.9%, respectively). Adverse events occurring among the elderly and younger participants were not statistically significant.

Conclusions: Survival, response, toxicity, and treatment-related mortality rates were not significantly different between the elderly and younger phase 1 trial participants in the no-transplantation setting. Regardless of the complex pharmacological profiles and logistical issues involved in treating the elderly population, our data imply that elderly study participants do at least as well as their younger counterparts, contributing to the justification of increasing the phase 1 trial enrollment of elderly patients.

Introduction

In the United States, the majority of all cases of cancer are diagnosed in people 65 years of age and older.1,2 Despite a growing elderly population, and a subsequently increasing cancer burden among the elderly, patients older than 65 years of age are frequently under-represented in oncology clinical trials.3,4 Limited data are available for this age group in terms of pharmacokinetics, toxicities, and the effectiveness of cancer treatments when compared with younger populations.5,6 In 1 trial of 16,396 patients, Hutchins et al1 reported that 25% of study participants were 65 years of age or older. Similarly, in another study of 28,766 persons with cancer who were enrolled in registration trials of novel cancer drugs or for new indications of cancer drugs already approved by the US Food and Drug Administration between 1995 and 2002, a total of 36% of patients were 65 years or older.7 Yet another study of 59,300 participants recruited in National Cancer Institute–sponsored, cooperative group trials between 1997 and 2000 reported that 32% of participants were 65 years of age or older.8

Barriers to clinical trial participation among elderly persons include stringent exclusion criteria, logistical challenges, and misconceptions among health care professionals and patients about the risks of participation.9 Cancer in geriatric patients may be difficult to treat because of multiple factors, including age-related physiological changes, significant comorbidities, and possible drug–drug interactions. These complexities may sway a health care professional’s decision to approach elderly patients with cancer for participation.
in clinical trials. In addition, many physicians cite lack of information on elderly patients, calling on the need to increase data in patients aged 65 years and older. Although the under-representation of elderly persons enrolled in clinical trials is gaining attention, the actual involvement of elderly persons with cancer in clinical trials has yet to reach appropriate proportions. Recently, however, some randomized trials have specifically evaluated the role of therapy in elderly persons with cancer.

With regard to phase 1 trials, information on the enrollment of elderly participants and their clinical outcomes is limited. Phase 1 trials are crucial for evaluating the safety profile of a drug, determining a safe dosage range, and identifying any adverse events. For the majority of study participants, phase 1 clinical trials are safe and beneficial. In addition, prognostic indices are being developed to better predict survival rates and treatment tolerances in phase 1 studies. However, the impact of age in predicting response, treatment tolerance, survival rate, and possible complications remains largely unknown.

In this study, we sought to analyze the clinical outcomes of elderly participants (defined as age ≥ 65 years) enrolled in phase 1 clinical trials at H. Lee Moffitt Cancer Center & Research Institute (Tampa, Florida) and compared their results with those of younger study participants (defined as age < 65 years).

Methods
All consecutive, single-center, phase 1 oncology trials initiated and completed at Moffitt Cancer Center between 1997 and 2007 were included in this analysis. The dataset was included until 2007 to primarily focus on chemotherapeutic trials. All trials were registered and received Institutional Review Board approval. All patients who gave informed consent to participate on a phase 1 study by December 31, 2007, were included on an intent-to-treat basis (ie, regardless of whether they received the study regimen). Patients who withdrew consent prior to receiving the study drug were not included in the cohort.

Data Sources
An OnCore system (Forte Research Systems, Madison, Wisconsin) database was used to generate the list of phase 1 trials conducted at Moffitt Cancer Center. Patients who consented to more than 1 clinical trial during the course of therapy were considered for the first Moffitt Cancer Center–only trial for which they received treatment. The Moffitt Cancer Center cancer registry database, case report forms (CRFs) containing original trial data, and electronic medical records (EMRs) were data sources used to extract individual patient data.

Data Extraction
Data were extracted using a standardized data extraction form. Variables of interest included demographic information, relevant dates for trial participation (enrollment, on treatment, off treatment, off study, and last contact), vital status, response, off-study reason, and toxicity grades and types. Random reviews of the dataset were performed to ensure accuracy of the data collection. More than 10% of the data was reviewed for accuracy.

Information on survival was primarily extracted from the cancer registry data. We supplemented and cross-referenced these data with the CRFs and EMRs. Data on response rate were extracted directly from the CRFs or EMRs for trials using the assessment noted by investigators. Investigator assessment was utilized for treatment decision-making on the trial and was considered accurate. For trials enrolling patients with solid tumors, investigators used the Response Evaluation Criteria in Solid Tumors for response assessment. Investigators used disease-specific response criteria for assessment in hematological malignancy trials. The CRFs for 1 myelodysplastic syndrome trial reported responses in terms of major and minor erythroid responses rather than complete and partial responses, among others. For consistency in reporting, we used the guidelines suggested by Cheson et al to convert these responses.

We extracted data on toxicities assessed by investigators according to the Common Toxicity Criteria (although the exact version varied depending on when the protocol was originally initiated) directly from CRFs or EMRs. Because toxicities were reported as adverse events (AEs) in CRFs, we extracted data for all grades 3, 4, and 5 AEs and noted whether they were attributed to treatment. Grade 3/4 toxicities were defined as being severe to life threatening and either definitely, probably, or possibly attributed to the study drug.

We used 2 methods to calculate mortality rate. Any death within 30 days following the administration of the last dose of the study drug was considered to be the 30-day mortality rate. The second method employed a direct extraction of the data from the CRFs or EMRs on death attributed to treatment. We reported both methods to account for patients who succumbed to disease within 30 days of being withdrawn from the study due to disease progression without having experienced any treatment toxicity.

Statistical Analysis
The outcomes of this study were overall survival (OS) rate, overall response rate (ORR), any grade 3/4 toxicity, and treatment-related mortality and 30-day mortality rates. For the purpose of this anal-
ysis, patients 65 years of age and older were considered to be elderly. Although analysis for benefits (ie, survival and response rates) was performed on an intent-to-treat basis, analysis for harms (ie, toxicities and treatment-related mortality rates) was performed per protocol. We planned a priori subgroup analyses on outcomes according to disease and treatment categories (eg, transplantation vs no-transplantation setting).

Survival was calculated using the Kaplan–Meier method from date of enrollment to last date of contact or death. A log-rank test was used to compare differences in survival between the subgroups. Differences in response rates and toxicity grades were calculated using the chi-square and Jonckheere–Terpstra tests, respectively. All reported P values were 2 sided, and a significance level of .05 was used. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

Study Selection

Between 1997 and 2007, a total of 147 phase 1 trials were opened at Moffitt Cancer Center. Of these, 108 were excluded due to multi-institution involvement, resulting in 39 trials (31 no-transplantation and 8 transplantation trials) for a total of 1,162 study participants at Moffitt Cancer Center alone (Fig 1). These study participants formed the intent-to-treat cohort. The median age in this cohort was 59 years (range: 18–91 years). Of the 1,162 study participants, 91% (n = 1,057) received treatment on study, 4.5% (n = 52) never received treatment, and 4.6% (n = 53) received an alternative treatment off study. Reasons for study participants not receiving treatment during the clinical trial included death, insurance issues, and the initiation of other therapies.

Baseline Characteristics

Table 1 lists the baseline characteristics of participants included in this study. Of the entire cohort (N = 1,162), 32.7% (n = 380) were elderly. The median ages of the elderly and younger participant co-

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Participants</th>
<th>Age &lt; 65 y (%)</th>
<th>Age ≥ 65 y (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>782 (67.3)</td>
<td>380 (32.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>385 (49.2)</td>
<td>133 (35)</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>397 (50.8)</td>
<td>247 (65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>53 (18–64)</td>
<td>69 (65–91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>303 (38.7)</td>
<td>107 (28.2)</td>
<td>.0005</td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>479 (61.3)</td>
<td>273 (71.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent transplantation</td>
<td>295 (37.7)</td>
<td>65 (17.1)</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>No transplantation</td>
<td>487 (62.3)</td>
<td>315 (82.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type of treatment

- Chemotherapy alone: 393 (50.3) vs 232 (61.0), P < .0001
- Chemotherapy + transplantation: 295 (37.73) vs 65 (17.1)
- Immunotherapy: 14 (1.8) vs 17 (4.5)
- Gene therapy: 59 (7.5) vs 47 (12.4)
- Chemotherapy + radiation: 21 (2.7) vs 19 (5)

Disease category

- Hematological malignancies: 303 (38.7) vs 107 (28.2), P < .0001
- Lung cancer: 99 (12.7) vs 70 (18.4)
- Melanoma and other skin cancer: 83 (10.6) vs 43 (11.3)
- Gastrointestinal cancer: 74 (9.5) vs 73 (19.2)
- Breast cancer: 63 (8.1) vs 7 (1.8)
- Renal cancer: 31 (4.0) vs 21 (5.5)
- Hepatocellular carcinoma: 21 (2.7) vs 11 (2.9)
- Soft-tissue sarcoma: 17 (2.2) vs 5 (1.3)
- Sarcoma: 16 (2.0) vs 3 (0.8)
- Gynecological cancer: 16 (2.0) vs 2 (0.5)
- Mesothelioma: 10 (1.3) vs 19 (5)
- Cancer of the endocrine glands: 9 (1.1) vs 5 (1.3)
- Other: 40 (5.1) vs 14 (3.7)

Table 1. — Characteristics of the Volunteer Cohorts
horts were 69 years (range: 65–91 years) and 53 years (range: 18–64 years), respectively. A single study evaluating chemotherapy in 9 participants with non–small-cell lung cancer exclusively enrolled elderly volunteers (defined as age ≥ 70 years). In the elderly population (n = 380), hematological malignancies represented 28.2% (n = 107) of cancers, gastrointestinal cancers accounted for 19.2% (n = 73), and lung cancer accounted for 18.4% (n = 70). In the younger population (n = 782), hematological malignancies, gastrointestinal cancers, and lung cancer were present in 38.7% (n = 305), 9.5% (n = 74), and 12.7% (n = 99) of the study participants, respectively. These differences are likely secondary to the age distribution of the respective diseases. Trials evaluating chemotherapy-only regimens enrolled 61% (232/380) of elderly patients as compared with 50.3% (393/782) of younger patients. Trials of stem cell transplantation enrolled 17.1% and 37.7% of elderly and younger patients, respectively.

**Efficacy Outcomes**

**Response Rates:** Among the study participants in the no-transplantation cohort, the ORR was 14%; 5.7% of study participants achieved complete response (CR) and 8.2% of achieved partial response (PR; Table 2). In addition, 30.4% of study participants achieved stable disease (SD). Response could not be evaluated in 15.4% of study participants. The primary reason for being unable to evaluate response included death or withdrawal from the study prior to restaging scans, screening failure, or the initiation of alternative therapies.

Among the elderly study participants in the no-transplantation cohort (n = 315), the ORR was 15.2% (CR: 7.3%; PR: 7.9%) and 33.7% had SD. The clinical benefit rate (CR + PR + SD) was 48.9%. Among younger study participants in the no-transplantation cohort (n = 487), the clinical benefit rate was 41.5%; CR was seen in 4.7%, PR in 8.4%, and SD in 28.3%. The differences in response rates were not statistically significant between the 2 age groups (P = .40).

Among the study participants who received stem cell transplantation, CR, PR, and SD were observed in 23.1%, 27.7%, and 23.1% of the elderly study participants, respectively. Progressive disease (PD) was observed in 1.5% of study participants, and 24.6% were not evaluable. Among the younger study participants, the ORR was 57.3% (CR: 31.5%; PR: 25.8%). SD was reported in 18.6% of these study participants and 7.5% had PD.

**Overall Survival:** In the no-transplantation group, the median OS rate was 10.9 months (95% confidence interval [CI]: 8.9–13.1) in the elderly cohort and 8.8 months (95% CI: 7.9–10.3) in the younger cohort (Fig 2; see Table 2). The difference in survival rates between the 2 age groups was not statistically significant (hazard ratio [HR] 0.89; 95% CI: 0.76–1.04; P = .145). No differences in the 2 age groups were seen on multivariable analysis. Tumor category (solid tumor vs hematological malignancy), sex, and type of treatment were significantly associated with outcomes in the multivariable analysis (Table 3).

In the transplantation group, elderly study participants had worse OS rates than younger study participants (HR 1.64; 95% CI: 1.17–2.29; P = .004). The median OS rate was 32.9 months in the elderly group and 44.9 months in the younger group. In the multivariable analysis, age and type of tumor were significantly associated with survival (see Table 3). When including both the transplantation and no-transplantation study cohorts, the OS rate was higher in younger study participants than in the elderly (median OS: 15.8 vs 13.4 months; P = .002).

**Toxicity Outcomes**

Among the elderly participants, 31% and 30% of them experienced grade 3 and 4 toxicities, respectively. Grade 3 and 4 AEs were observed in 31.7% and 34% of the younger study participants, respectively. No significant differences were seen in grade 3 and 4 AEs between the elderly and younger cohorts (P = .093). In the no-transplantation group, the incidences of grade 3 and 4 AEs among the elderly were 29.5% and 28.2%, respectively, and the incidences of grade 3

### Table 2. — Median Survival and Response Rates

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Participants</th>
<th>Median Survival Rate, mo (95% CI)</th>
<th>Response Rates (%)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NEa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>782</td>
<td>15.8 (14.0–8.0)</td>
<td>14.8</td>
<td>15.0</td>
<td>24.7</td>
<td>30.3</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>380</td>
<td>13.4 (11.3–16.2)</td>
<td>10.0</td>
<td>11.3</td>
<td>31.8</td>
<td>29.0</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td><strong>Transplantation vs no transplantation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Transplantation</td>
<td>360</td>
<td>40.5 (37.6–48.5)</td>
<td>30.0</td>
<td>26.1</td>
<td>19.4</td>
<td>6.4</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>&lt; 65 y</td>
<td>295</td>
<td>44.9 (39.0–53.5)</td>
<td>31.5</td>
<td>25.8</td>
<td>18.6</td>
<td>7.5</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>≥ 65 y</td>
<td>65</td>
<td>32.9 (22.4–39.9)</td>
<td>23.1</td>
<td>27.7</td>
<td>23.1</td>
<td>1.5</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>No transplantation</td>
<td>802</td>
<td>9.5 (8.6–10.9)</td>
<td>5.7</td>
<td>8.2</td>
<td>30.4</td>
<td>40.4</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>&lt; 65 y</td>
<td>487</td>
<td>8.8 (7.9–10.3)</td>
<td>4.7</td>
<td>8.4</td>
<td>28.3</td>
<td>44.2</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>≥ 65 y</td>
<td>315</td>
<td>10.9 (8.9–13.1)</td>
<td>7.3</td>
<td>7.9</td>
<td>33.7</td>
<td>34.6</td>
<td>16.5</td>
<td></td>
</tr>
</tbody>
</table>

* A portion of patients were NE for response due to several reasons, including death prior to restaging scans, withdrawal from study prior to scans, alternate therapy, and screening failure.

CI = confidence interval, CR = complete response, NE = not evaluable, PD = progressive disease, PR = partial response, SD = stable disease.
and 4 AEs among the younger population were 30.6% and 27.3%, respectively. Table 4 lists the AEs of at least grade 3 experienced by all of the phase 1 clinical trial cohorts in the no-transplantation setting.

Gastrointestinal and metabolic nutritional toxicities were observed at higher rates in younger study participants, whereas general toxicities were higher in the elderly study participants. The toxicities were similar in the study participants undergoing transplantation; 78.6% of the elderly and 76.9% of the younger study participants experienced AEs of grade 3 or higher ($P = .418$).

**Treatment-Related Mortality**

For those in the no-transplantation group, the 30-day mortality rate was 10% (30/300) among the elderly study participants and 9.2% (43/468) in the younger study participants, whereas treatment-related mortality rates were 1% (3/300) and 0.9% (4/468) for the elderly and younger cohorts, respectively. The differences between these rates were not statistically significant.

**Discussion**

In our study cohorts (39 trials totaling 1,162 study participants), 32.7% of study participants were at least 65 years of age. Only 1 of the 39 studies evaluated was exclusively aimed at enrolling elderly participants. To align the discrepancy between the limited number of trials focused on elderly participation and the increasing number of elderly patients, more trials specifically designed for an elderly population are necessary.

Due to the large percentage of patients with cancer aged 65 years and older, it is imperative to evaluate the safety and tolerability of possible treatments in elderly patients. This must be underscored by the fact that pharmacokinetics and pharmacodynamics significantly differ from those in young patients due to age-related biological changes. Furthermore, elderly patients frequently have more comorbidities and higher rates of medication use than their younger counterparts, thus making treatment options for cancer more complicated.
Several prognostic scores have been developed to predict clinical outcomes in patients participating in phase 1 clinical trials. The Royal Marsden Hospital prognostic score includes elevated lactate dehydrogenase levels, hypoalbuminemia, and more than 2 sites of metastasis as variables associated with poor prognosis. Wheler et al further validated the score at the phase 1 clinic at the MD Anderson Cancer Center (Houston, Texas). Gastrointestinal tumor type and an Eastern Cooperative Oncology Group performance status of 1 or more were both included as additional factors associated with prognosis. Study participants with none of these risk factors had a median OS rate of 24 months compared with 4.1 months in study participants with the highest risk scores. However, none of these scores included age as a prognostic factor.

To our knowledge, only 1 previous study has reported on survival rates in geriatric patients participating in phase 1 clinical trials. Zafar et al found that elderly patients who enrolled in clinical trials (n = 95) had a median OS rate of 8.4 months compared with elderly patients who consented but were ineligible for study inclusion (n = 114) whose median OS rate was 3.9 months.

We performed a systematic analysis of all consecutive oncology phase 1 trials conducted at Moffitt Cancer Center between 1997 and 2007 and compared the benefits and harms in elderly and younger study participants. In the no-transplantation setting, transplantation is comparable with results shown in previous studies reporting on the outcomes of participants enrolled in phase 1 clinical trials. Among the patients undergoing stem cell transplantation, age has been demonstrated to be a major prognostic factor in several retrospective studies. Our results are consistent with prior studies, suggesting that elderly patients have significant worse survival rates than younger patients.

Our findings support the notion that age should not be used as a prognostic factor, particularly when determining eligibility for phase 1 clinical trials. Furthermore, our finding of a median survival rate of 10.9 months in elderly study participants not undergoing transplantation is comparable with results shown in previous studies reporting on the outcomes of participants enrolled in phase 1 clinical trials.

### Limitations

There are several limitations to our study, including its retrospective nature. All trials included were from Moffitt Cancer Center, thus providing a single-center perspective. It is unknown whether the data would differ if data from other centers were included. Other limitations include the high probability for selection bias among elderly patients. The low enrollment numbers of elderly patients, relative to their proportion of disease, may lead to enrollment of only the healthiest of elderly patients. This possible bias is impossible to accommodate for and difficult to assess.

Our study primarily included treatment with cytotoxic or immunotherapeutic agents rather than targeted agents, which are much more common today. However, the prognostic scores mentioned above that do not include age have been validated in patients...
receiving cytotoxic as well as targeted agents.

Although more studies are needed, our data demonstrate that clinical outcomes, effectiveness, and rates of toxicities are not substantially different between elderly and younger study participants in phase 1 clinical trials.

Conclusions
Participation in phase 1 clinical trials should not be hindered by age. Rather, efforts should be made to increase clinical study participation among the elderly patient population so as to decrease the gap between those who bear the disease burden and those enrolled in clinical trials. By accumulating evidence in the elderly population, health care professionals may be encouraged to treat their elderly patients in an appropriately aggressive manner. As the US population continues to age, information on treatment options for elderly persons has become — and will continue to be — increasingly crucial to patient care.

References

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